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Tiny bubbles

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SINCE DECOMPRESSION SICKNESS (DCS) was first described, the elusive nature of its pathophysiology has been a challenge. It is generally thought that intravascular and extravascular bubbles are responsible for a host of downstream effects that cause the constellation of clinical findings known as DCS. Through the years, theories of gas exchange and bubble formation have been hypothesized, tested, and modified to increase safety and performance in hypo- and hyperbaric decompression excursions. Although perhaps not ideal, this approach has been necessary given the technical limits in a growing field that needs real-time application. In this issue, Wilbur et. al. (9) present what could potentially provide a technical solution to the long hypothesized but ultimately evasive micronuclei. This unique blend of theory and empiricism has certainly advanced the field, but large gaps in our understanding of the basic mechanisms of bubble formation (and hence DCS) remain.

Early studies in decompression theory demonstrated that supersaturation (even at extreme changes in ambient pressure) alone was insufficient to generate bubbles. As early as 1912, Hill postulated the need for weak "points" in a fluid for bubbles to form (7). Through the years, these weak "points" evolved through observations and sound research into the micronuclei concept. Currently, micronuclei are defined as a small particle <10 μm in diameter that is filled with gas. These small bubbles would satisfactorily explain larger bubble formation at relatively small pressure changes observed in decompression. If bubbles then need micronuclei to form their origin, the micronuclei should present an ideal therapeutic target in the prevention of DCS (8).

Since its theoretical inception, a vast body of sound investigations has strongly supported the micronuclei concept but reliably fallen short of actually proving its existence. The reliance of a basic theory of bubble formation on a theoretically necessary entity that has not been conclusively demonstrated has been an interesting story in decompression research. Initially, studies applied to inanimate fluids, excised tissue, and ex vivo blood supported the existence of micronuclei. The observation that fewer bubbles were formed in a liquid that had been subjected to "denucleation" (such as centrifugation to "crush the nuclei") compared with a liquid that had not been denucleated was not only encouraging but established a rationale for whole animal testing.

Evans utilized translucent shrimp to validate and strengthen the micronuclei case by demonstrating a significant reduction in bubble formation when shrimp were compressed to 400 atm of pressure before decompression (6). Vann then provided further evidence of micronuclei in rats by rapidly compressing air breathing rats to 1,000 fsw before decompression after 2 h at 240 fsw. Vann's results demonstrated significantly less DCS with this strategy, supporting the existence of the micronuclei and, more importantly, presenting a potential therapeutic target in other mammalian species (8).

In the current millennium, experiments directed at the micronuclei concept have yielded authentic practicality in enhancing the safety and performance capacity of pressure excursions. The potential of micronuclei as a therapeutic target has been hypothesized and examined in oxygen prebreathing, exercise, and nitric oxide donors.

Recognizing that micronuclei depleting pressure excursions are not easily feasible or even desired, alternative methods to limit micronuclei through gas-changing techniques have been tested. If micronuclei are gas filled, then it stands to reason that a change in its surrounding gas partial pressure (such as using high fractions of inspired oxygen) would favor the shrinking and dissolution of the micronuclei. In small animal models, surface and hyperbaric oxygen used before full compression and decompression have decreased bubbles (2) and decreased evidence of spinal cord injury in the rat (1).

Theories of exercise in relation to bubble formation and DCS could certainly benefit from proving the existence of micronuclei. It has been well established that strenuous exercise 24 h before an 18-m dive significantly decreases intravascular bubbles in man (5). Whereas strenuous exercise closer to dive time, or >48 h from dive time, confers no benefit in the way of decreasing bubbles. And exercise immediately before diving appears to worsen the bubble load in hypobaric excursions (4). The micronuclei (or changes in rheological properties) has been invoked to explain the nature of the benefit (or harm) in this fairly precise timing of exercise relative to dive time.

Finally, observations regarding the timing of exercise in both humans and animals before diving have led to simple pharmacological manipulation in the form of nitric oxide donors that have decreased bubble counts in humans (and presumably decreased DCS risk) (10).

In this issue of *Journal of Applied Physiology*, Wilbur et. al. (9) describe the technique of dual-frequency ultrasound (DFU) in recognizing signals consistent with micronuclei after normobaric exercise. The availability of a technique that could potentially shed much needed light on bubble formation is welcomed. A technique that could *quantify* anticipated bubble formation would be downright dazzling.

Certainly much work remains to be done. The signals reported here by Wilbur et. al. may have alternative explanations, such as lipid transport, and need to be confirmed with other techniques. If these signals are in fact gas-filled micronuclei, their composition and distribution would also be of more than curious interest (3). Last, the demonstration that recent experiments designed specifically to examine micronuclei have, in fact, decreased micronuclei quantities

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could lead to entirely new directions for decompression research.

I am (cautiously) optimistic that the signals reported are gas-filled micronuclei. If such is the case, it would be a facile leap to envision improved decompression schedules as a result of this work and may significantly move the field of decompression theory beyond the comfortable and well worn empiricism we all know too well.

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